Chapter 10

Vestibular-evoked myogenic potentials

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Abstract

The vestibular-evoked myogenic potential (VEMP) is a short-latency potential evoked through activation of vestibular receptors using sound or vibration. It is generated by modulated electromyographic signals either from the sternocleidomastoid muscle for the cervical VEMP (cVEMP) or the inferior oblique muscle for the ocular VEMP (oVEMP). These reflexes appear to originate from the otolith organs and thus complement existing methods of vestibular assessment, which are mainly based upon canal function. This review considers the basis, methodology, and current applications of the cVEMP and oVEMP in the assessment and diagnosis of vestibular disorders, both peripheral and central.

BACKGROUND

The vestibular apparatuses are small organs that lie within the temporal bone and are therefore inaccessible to direct assessment in human subjects. The potent motor effects arising from the labyrinths were first appreciated by means of local destruction (Camis, 1930), including the unexpected finding that destruction bilaterally had less severe effects than unilateral lesions. The vestibular end organs are innervated by the superior and inferior divisions of the vestibular nerve (Shute, 1951). The utricle, horizontal canal, and superior canal pass their afferents through the superior division of the nerve and the saccule and the posterior canal via the inferior division. A small portion of the saccular afferents travel via Voit’s nerve to the superior division of the nerve (Gacek and Rasmussen, 1961). Vestibular afferent projections terminate either in the vestibular nuclei or the vestibulocerebellum (Wilson and Peterson, 1978). The major descending tracts are the medial and lateral vestibulospinal tracts, but projections to the spinal cord also travel through reticulospinal pathways (Goldberg et al., 2012).

Vestibular sound sensitivity

One notable early experiment indicating that the vestibular apparatus might respond to (loud) sounds was the work by von Békésy (1935). A variety of modulated tones were used in normal volunteers and an estimate made of the sound intensity required for vestibular activation – sound pressures of the order of 500–1000 dyn/cm² (equivalent to 128–134 dB sound pressure level (SPL)). Von Békésy showed the effect was not due to cochlear activation by transiently deafening his subjects.

In 1963 Bickford et al. reported a “new audio motor system in man” with latencies of 8–10 ms in cervical muscles that clearly distinguished it from startle (25 ms) and voluntary responses. This report importantly recognized that the short latency implied an oligosynaptic pathway, identified the dependence upon tonic muscle activation, and also that the response was of myogenic (electromyogram: EMG) origin. It soon became evident that the response required an intense click stimulus and did not depend upon the cochlea, thus an origin from vestibular

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receptors was proposed (Bickford et al., 1964; Cody et al.,
1964). Although initially presented mainly as a source of
unwanted artefact, Cody et al. (1964) recognized the pos-
sible value of the test and clearly distinguished its prop-
erties from those of the vertex response evoked by sound.
Townsend and Cody (1971), based upon their clinical
observations, proposed an origin from the saccule.

THE CERVICALVESTIBULAR-EVOKED
MYOGENIC POTENTIAL

Properties
Current interest in the vestibular-evoked myogenic
potential (VEMP) as a clinical investigation was
prompted by the report of Colebatch et al. (1994), who
moved the recording site from the inion to the sternoclei-
domastoid (SCM). The SCM provided two advantages
over the inion: the reflex could be unambiguously attrib-
ted to a single muscle and the laterality could be easily
determined. The authors demonstrated that the response
to loud clicks consisted of two separable parts: an early
positive–negative response (p13-n23) which occurred
ipsilaterally to the ear stimulated and a later, bilateral
response. Studies of patients with selective auditory
lesions supported a vestibular origin for the p13-n23 potential. The high sound threshold and
dependence upon tonic muscle activity, previously
reported for the inion response, were confirmed. SCM
activity was measured using full-wave rectified EMG
activity and the change in amplitude of the p13-n23
response with the level of rectified EMG was remarkably
linear. The findings of Young et al. (1977) of a lower
threshold for saccular receptors to sound, as well as the
report by Didier and Cazals (1989) of saccular afferents
being excited by loud clicks in guinea pigs, led the
authors to propose a saccular origin for the click-evoked
cervical VEMPs (cVEMPs).

Once a reliable response pathway had been defined, other methods of stimulation were investigated. Clicks
are not the only form of air-conducted (AC) sound that
has been shown to be effective and tone bursts have been
used to investigate the tuning of the response. Here caution
is required, because the middle ear has potentially signif-
ificant filtering effects and a distinction needs to be made
between tuning of the middle-ear–vestibular system as
distinct from the vestibular receptors themselves. Fre-
cency tuning of the cVEMP has been widely studied
(e.g., Murofushi et al., 1999; Todd et al., 2000;
Welgampola and Colebatch, 2001a; Akin et al., 2003),
with the conclusion that there is a broad range of tuning,
maximal around 400–1000 Hz, for the combined middle-
ear–vestibular response. Stimuli within this resonant fre-
cquency range are therefore more efficient and allow lower
intensities to be used (Rosengren et al., 2009).

Soon afterward it was found that an impulsive bone-
conducted (BC) stimulus, consisting of a tap to the fore-
head using a tendon hammer, also evoked short-latency,
bulateral (for midline taps), positive–negative responses
in SCM (Halmagyi et al., 1995). BC sound/vibration
(Sheykholeslami et al., 2000) was subsequently also
shown to be effective. These forms of stimulation were
thought to have their greatest application in subjects with
conductive hearing loss, a condition which severely
attenuated AC-evoked VEMPs. Welgampola et al.
(2003), using a standard B71 bone conductor applied just
behind the ear, showed that vestibular-dependent, short-
latency biphasic responses were evoked bilaterally,
although larger ipsilaterally (Fig. 10.1). The hearing
level (HL) intensity of the BC stimulus was much lower
than for AC, implying that it was relatively more effect-
ve for vestibular receptors than for cochlear ones
(Welgampola et al., 2003). A broadly similar tuning
curve to AC stimulation was shown, but with low-
frequency enhancement. The latter could not be fully
defined due to limitations of the B71 output. More pow-
erful minishakers, with wider-frequency responses than
audiometric bone vibrators, have allowed more detailed
investigation of frequency and impulsive effects. For
example, using a minishaker, Todd et al. (2008a) showed
enhancement of cVEMP amplitude with lower frequen-
cies of stimulus, with a peak around 100 Hz. Although
the tendon hammer has the virtue of simplicity, impulses
derived from a minishaker or other vibrator have at least
two clear advantages – the intensity can be altered with-
out compromising the trigger and both positive (motor
movements toward subject, like the tendon hammer)
and negative (motor movement away from subject) forces
can be applied, allowing the direction of acceler-
ation to be independent of the side of application.

The final type of VEMP stimulus is galvanic vestib-
ular stimulation (GVS) – a low-intensity DC current,
which has been used for many years to activate the ves-
tibular end organs (e.g., Fitzpatrick and Day, 2004).
A current of about 4 mA, 2 ms long, and delivered to
the mastoid process is effective and short enough to
avoid severe stimulus artefact. However, a special sub-
traction technique (of traces with relaxed versus con-
tacted SCM muscle) is required to remove the
remaining stimulus artefact (Watson and Colebatch,
1998). Irregularly discharging afferents are most sensi-
tive to this stimulus and the effect appears to be at the
level of the nerve afferent ending (Goldberg et al.,
1984). As the stimulus is thought to activate the nerve
rather than the end organ, GVS-evoked VEMPs have
been proposed to potentially distinguish between recep-
tor and neural disorders (Murofushi et al., 2003),
although this may not hold for chronic disorders, as per-
manent receptor damage may change the sensitivity of
the vestibular nerve. However, due to the technical difficulty involved, VEMPs evoked by GVS have not been widely adopted in clinical contexts.

Electrophysiologic investigations in animal preparations have confirmed the presence of a short-latency inhibitory postsynaptic potential in the motoneurones innervating the ipsilateral SCM in response to stimulation of both the saccule and the utricle (Kushiro et al., 1999). Only utricular afferents had an effect on the contralateral side, evoking an excitatory postsynaptic potential. The latter may explain the short-latency crossed negativity seen in some normal subjects in response to acoustic stimulation (Welgampola and Colebatch, 2001b). The pathway to the SCM motoneurones appears to be mediated through the medial vestibulospinal tract, similar to the projection from the semicircular canals (Fukushima et al., 1979; Fig. 10.2).

**Population responses and age effects**

Welgampola and Colebatch (2001b) carried out an early study on normative values for cVEMPs. They examined 70 healthy adults, aged 25–85 years old, using clicks, head taps, and galvanic-evoked responses. There was an increase in threshold for clicks with age, associated with a reduction in corrected amplitudes (peak-to-peak unrectified values divided by the mean rectified EMG), such that the average amplitude for the eighth decade was less than half that for the third. Over the age of 60, responses were sometimes absent on one side, but below 60 the range of amplitude asymmetry ratios was less than 35%. The mean p13 latency was 12.0 ms and showed no correlation with age. Tap-evoked cVEMPs were larger and fell more slowly with age, while galvanic-evoked reflexes also declined significantly with age.
Welgampola and Colebatch proposed that degeneration of end organs and their afferents was likely to be the basis of the age-related changes. Subsequent studies have confirmed the significant age effects on cVEMP amplitude and threshold (Basta et al., 2007; Brantberg et al., 2007; Rosengren et al., 2011; Piker et al., 2013). Further analysis of age effects showed two patterns of change with age (Colebatch et al., 2013). Responses to high-frequency stimuli (AC or BC 500 Hz) fell significantly with age, on average by 12% per decade over the age of 20, while taps and impulsive stimuli, with low-frequency content (<100 Hz), were significantly less affected.

Limited information is available about the properties of VEMPs in infants and children, although testing is clearly possible with pediatric subjects and the technique appears to be well tolerated. Sheykholesami et al. (2005) demonstrated that it is possible to record cVEMPs from normal neonates and the cVEMP is present in children of all ages (Picciotti et al., 2007; Zhou et al., 2014). Specific techniques are needed to ensure adequate SCM activation in younger children, but the technique has proven useful in diagnosis (Zhou et al., 2014).

**The Ocular Vestibular-Evoked Myogenic Potential**

**Properties**

Stimulation of the vestibular organs with sound, vibration, or galvanic current produces small eye movements that can be measured with sensitive magnetic coil systems. The ocular VEMP (oVEMP) represents the electric activity produced by the extraocular muscles during this eye movement (Todd et al., 2007; Welgampola et al., 2009). Although the evoked eye movements are very small, oVEMPs can be recorded from surface electrodes placed close to the eyes, as the abrupt nature of the stimulus produces a synchronous change in muscle activity. Studies have shown that the surface potential is distinct from the corneoretinal dipole (Rosengren et al., 2005; Todd et al., 2007) and is not a blink reflex (Smulders et al., 2009). oVEMPs are generally largest when recorded from beneath the eyes during up-gaze (e.g., Govender et al., 2009), and under these conditions originate primarily from the inferior oblique (IO) muscle (Weber et al., 2012).

The oVEMP consists of a series of waves beginning at short latency. When a single ear is stimulated with AC
sound, the clearest response is recorded under the contra-
lateral eye, suggesting a predominantly contralateral pro-
jection (Chihara et al., 2007). The response begins at
approximately 7 ms and its first peak occurs at approxi-
mately 10 ms (Fig. 10.3). The polarity of the initial peak
is negative for most of the commonly used vestibular
stimuli, and the response is therefore termed n10. The
n10 is followed by a positive peak at approximately
15 ms (p15) and further negative and positive peaks at
intervals of about 5 ms. Recordings from patients with
bilateral vestibular loss usually show complete absence
of responses, suggesting that all of the peaks are
vestibular-dependent (Todd et al., 2009). In patients with
unilateral vestibular loss, activation of both ears simulta-
neously with BC stimulation evokes an n10 response
predominantly under the eye opposite the intact ear,
again indicating a contralateral projection (Iwasaki
et al., 2007). There is often a small residual negativity
under the ipsilateral eye (Todd et al., 2007), possibly
originating from nearby extraocular muscles, and the
later potentials are also usually preserved in these
patients (Iwasaki et al., 2007).

The properties of the oVEMP change with gaze
direction, most likely due to changing contributions
from the extraocular muscles. As myogenic potentials
spread widely around the head (Rosengren et al.,
2005; Todd et al., 2008b), a bipolar montage, with elec-
trodes placed beneath the eyes, is used to provide a
more selective recording from the inferior extraocular
muscles (Todd et al., 2007). Using this electrode mon-
tage, the n10-p15 response is largest during superome-
dial gaze (Chihara et al., 2007; Govender et al., 2009).

oVEMP responses tend to become smaller and less prev-
nalent with increasing age (e.g., Iwasaki et al., 2008;
Tseng et al., 2010; Rosengren et al., 2011; Agrawal
et al., 2012; Chang et al., 2012). This is a particular prob-
lem for oVEMP evoked by AC sound, as they are typ-
ically smaller than those evoked by BC stimulation,
leading to a high rate of absent responses in normal older
subjects (Piker et al., 2011) and reducing the clinical util-
ity of the AC reflex. Age effects have also been shown for
oVEMP evoked by BC stimulation, but appear to
depend upon the type of stimulus. oVEMPs evoked by
tendon hammer taps and low-frequency pulses delivered
with a minishaker are relatively robust against age effects
(Nguyen et al., 2010; Colebatch et al., 2013), while those
evoked by sine waves and short-duration square waves
appear to be more susceptible (Iwasaki et al., 2008;
Chang et al., 2012). Effects of age have also been found
on oVEMP latency (i.e., prolonged peak latency with
increasing age: Rosengren et al., 2011; Chang et al.,
2012), but not symmetry (Tseng et al., 2010; Piker
et al., 2011). Gender does not appear to affect oVEMPs
evoked by sound or vibration (Piker et al., 2011;
Rosengren et al., 2011).
Similarly to the cVEMP, the mean preferred stimulus frequency for the oVEMP evoked by AC sound is around 500–1000 Hz (Chihara et al., 2009; Park et al., 2010; Murmane et al., 2011), while for individuals the best frequency can vary widely, between approximately 150 and 1500 Hz (Lewis et al., 2010; Zhang et al., 2011a). Overall, tuning is similar for both the oVEMP and the cVEMP, though a recent study reported concordance of only 43%, with discordant tuning nearly always resulting in higher preferred frequencies for the oVEMP (Taylor et al., 2012a). Fewer studies have examined the preferred stimulus frequency for BC oVEMP stimuli, although many clinicians use tendon hammers or square-wave pulses rather than sine waves. The available studies suggest that the best frequency is somewhat lower than that for AC sound, around 100–250 Hz (Chihara et al., 2009; Todd et al., 2009; Donnellan et al., 2010; Zhang et al., 2012a).

The site of stimulation and stimulus polarity have significant effects on the properties of the BC oVEMP. In particular, altering the direction of head acceleration has profound effects on the reflexes (e.g., Todd et al., 2008a; Lin et al., 2009; Holmeslet et al., 2011; Jombik et al., 2011). Several studies have examined the effects of gravity on the oVEMP, by altering the orientation of the head and body during the test in either the pitch (Govender et al., 2009; Wang et al., 2014) or roll axes (Iwasaki et al., 2012; Gürkov and Kantner, 2013; Taylor et al., 2014); however, there is currently no consensus about potential gravity effects.

**ELECTROGENESIS OF VEMPs**

The cVEMP is produced by a brief inhibition of the ipsilateral SCM muscle. Colebatch and Rothwell (2004) recorded the activity of single motor units in normal human volunteers and found a reduction or gap in firing in the SCM ipsilateral to the AC sound or cathodal galvanic stimulus. The inhibition occurred at a similarly short latency (~12 ms) to the surface p13 peak and had a very short duration (~3–4 ms). Although the cVEMP recorded at the surface is biphasic, both the p13 and n23 components are likely to be produced by the single period of muscle inhibition (Fig. 10.4), as both potentials are correlated with the magnitude and duration of the initial motor unit inhibition, rather than any increase or recovery of activity (Rosengren et al., 2015). In addition, mapping studies have shown that the p13 response behaves like a traveling wave, i.e., the latency of the p13 increases with increasing distance of the recording electrode from the motor point, and thus the potential represents the progressive spread of inhibition of motor unit firing along the muscle toward the tendons (Colebatch, 2012). In contrast, the n23 response behaves more like a standing wave, i.e., the latency remains relatively constant as the electrode is moved and the surface potential is mainly produced by the momentary dipole generated by the arrival of the inhibitory response at the muscle–tendon junction (Lateva et al., 1996).

For the oVEMP, surface recordings under different stimulation and recording conditions suggested an origin predominantly in the IO muscle contralateral to the stimulated ear. Excitation of the IO muscle as the basis of the
oVEMP was recently confirmed by Weber et al. (2012), who recorded single motor unit responses evoked by AC and BC sound in the IO and IR muscles of normal subjects. The earliest responses in IO were excitatory and occurred at 10.5 and 13.3 ms for BC and AC sound, respectively. While the IR was also excited by the BC stimulus, responses in this muscle were delayed by 4–5 ms compared to the IO, suggesting that the muscles were reciprocally active and that the n10 surface response did not come from the IR muscle. The temporal profile of the IO motor unit response closely matched that of the surface oVEMP recorded during up-gaze, suggesting that, while contributions from the other extracocular muscles could not be ruled out, the oVEMP recorded beneath the eyes during up-gaze was primarily produced by an excitation of the IO muscle.

**AFFERENTS RESPONSIBLE FOR VEMPs**

There are several lines of evidence about which vestibular afferents are responsible for cVEMPs and oVEMPs. These include animal studies of the effects of AC and BC stimulation on vestibular afferents and the projections to the neck and eye muscles, and human studies of the effects of selective nerve lesions on the reflexes. Cautious interpretation is required, due to the different species and methods used in animal studies and the possibility of incomplete lesions in human clinical studies.

Studies have suggested that the otoliths, and the saccule in particular, are especially sensitive to AC sound. Young et al. (1977) showed in squirrel monkeys that all of the vestibular organs could be activated by AC sound, though the saccule had the lowest threshold. Subsequent studies also demonstrated greater activation of otolith fibers by AC sound and have confirmed that it is primarily the irregular vestibular afferents that are affected (McCue and Guinan, 1994; Murofushi and Curthoys, 1997; Carey et al., 2004; Zhu et al., 2011, 2014; Curthoys et al., 2012). However, there is disagreement about the extent to which semicircular canal afferents are activated. Curthoys et al. (2012) reported that otolith afferents were much more sensitive than canal afferents, while Zhu et al. (2011, 2014) described a graded relationship, with the saccule being most sensitive and the posterior canal least sensitive (saccule > utricle > anterior canal > horizontal canal > posterior canal). Despite this debate about the normal ear in animals, there is clear evidence that semicircular canal afferents are activated by AC sound in the presence of an experimental third labyrinthine window (e.g., Carey et al., 2004). There is less animal evidence about the sensitivity of the vestibular organs to BC stimulation. Young et al. (1977) reported that the otoliths were less sensitive than the semicircular canals to skull vibration. In contrast, Curthoys et al. (2006) showed that the irregular fibers of both otoliths were preferentially activated, and vibration-sensitive afferents could be traced to both otoliths (Curthoys et al., 2012). As a result of the above evidence, VEMPs are considered to originate primarily in the otolith organs.

**cVEMP origins**

cVEMPs evoked by AC sound are thought to originate mainly in the saccule because of the higher sound sensitivity of the saccule compared to the other organs, combined with evidence from animal studies about the projections to the SCM neck muscles as well as studies in human subjects, including both normal subjects and patients with selective lesions of the superior and inferior nerves. All three semicircular canals and the utricle inhibit the ipsilateral SCM and excite the contralateral SCM, while saccular afferents inhibit the ipsilateral SCM, but have no known projection to the contralateral side (Kushiro et al., 1999; Uchino and Kushiro, 2011). As the cVEMP evoked by AC sound is usually a strictly unilateral inhibition of the ipsilateral SCM muscle, this is consistent with an origin from the saccule. However, the ipsilateral cVEMP is sometimes accompanied by a crossed excitatory response in the opposite SCM, albeit with smaller amplitude and higher threshold (Walgampola and Colebatch, 2001b). Based on the known SCM projections, this suggests that other organs sometimes contribute at higher intensities. As the otoliths are more sensitive to AC sound, the utricle is the most likely origin of this “crossed response.” However, in patients with third-window syndromes, the anterior semicircular afferents are thought to contribute to the observed large crossed responses (Watson et al., 2000; Rosengren et al., 2008). AC cVEMPs are usually preserved in patients with vestibular neuritis, which often selectively affects the superior nerve portion (e.g., Govender et al., 2011). Sheykholeslami and Kaga (2002) reported 7 patients with anomalies of semicircular canals who all had normal AC cVEMPs, supporting an otolith origin.

cVEMPs evoked by BC vibration or head taps are also thought to originate predominantly in the otolith organs. However, the relative contributions from the saccule and utricle have not been determined and may depend upon properties of the BC stimulus. As BC stimuli act directly on the vestibular hair cells through linear acceleration of the head and soft tissues within the skull, VEMPs evoked by BC stimulation are bilateral and highly dependent upon the direction of acceleration. In patients with complete vestibular loss in one ear, cVEMPs evoked by BC impulsive stimuli are often bilateral, with opposite polarity on the affected side, suggesting that the remaining
utricles and utricular fibers are predominantly of utricular origin for all stimuli. The oVEMP is similarly activated by both types of otolith fibers, and impulsive stimulation with 500 Hz and 100 Hz activated cVEMPs and oVEMPs. Their calculations showed that the AC 500 Hz cVEMP was predominantly of saccular origin, while the AC 500 Hz oVEMP was predominantly of utricular origin. Therefore, it is possible that the saccule also contributes to the oVEMP, or even provides the dominant input for the oVEMP. However, it is possible that the sacculus also contributes to the oVEMP, or even provides the dominant input with some types of stimuli, as the two otoliths are preferentially activated by linear acceleration in different directions (Fernández and Goldberg, 1976).

A recent study of patients with vestibular neuritis studied with AC and high- and low-frequency BC stimuli (Govender et al., 2015) was able to estimate the upper limits of contributions of saccular and utricular afferents to cVEMPs and oVEMPs. Their calculations showed that the AC 500 Hz cVEMP was predominantly of saccular origin, that BC 500 Hz and AC 500 Hz activated similar populations of otolith fibers, and impulsive stimuli activated utricular fibers most strongly. The oVEMP was predominantly of utricular origin for all stimuli.

**MECHANISM AND PHYSIOLOGIC ROLE**

Von Békésy (1935) proposed that eddy vortices might be the mechanism by which loud sound stimulated vestibular receptors, but the mechanism of action of AC stimuli is still not clear. The reduced thresholds for VEMP responses in patients with large vestibular aqueducts (Sheykholeslami et al., 2004; Merchant et al., 2007; Taylor et al., 2012b) raises the possibility that the normal sound sensitivity of vestibular afferents is in part a consequence of sound energy traveling from the oval window to the vestibular aqueduct (Merchant et al., 2007). McCue and Guinan (1994) confirmed the presence of polarization of responses to clicks as well as characteristic tuning curves. They subsequently proposed (McCue and Guinan, 1995) that the most likely candidates for this resonance were either the otolithic membrane (cf. Todd et al., 2009) or the sensory epithelium. BC stimulation of the otolith organs is likely to work through inertial accelerations of the otolith membrane, given that this is the method of physiologic activation by gravity. Support for this comes from the direction-specific effects of skull acceleration for both the cVEMP (Rosengren et al., 2009) and the oVEMP (Todd et al., 2007). Resonance around 100 Hz is present and can be modeled using properties of the utricle (Todd et al., 2009) and the isolated utricle shows a resonant peak between 300 and 400 Hz (Dunlap and Grant, 2014). Todd et al. (2009) also modeled the higher resonance frequencies shown for AC stimulation using properties of the saccule, and responses of the saccule in this range have been observed (e.g., Ashcroft and Hallpike, 1934).

VEMP responses are believed to be short-latency fragments of vestibulocollic and vestibulo-ocular reflexes (VOR) originating from otolith afferents (see above). Direct recordings of the eye movements induced by 500 Hz stimulation indicate that, while there is considerable interindividual variation, AC stimulation induces elevation, extorsion, and abduction of the contralateral eye, whereas BC stimulation at the mastoid with a similar stimulus induces depression, extorsion, and abduction (Todd et al., 2007; Welgampola et al., 2009). Given the evidence that irregularly discharging otolith afferents are the main source of VEMPs, it is to be expected that the reflex effects of VEMPs may be understood in terms of otolith-collic and otolith-ocular reflexes. Direct stimulation of the saccule and utricle produces different eye movements depending upon the region of macula stimulated (Fluur and Mellström, 1970a, b). Selective whole-nerve stimulation showed strong contralateral ocular rotation induced by utricular nerve activation, as well as the ability to follow high frequencies of stimulation (Suzuki et al., 1969).

VORs, the best known being the rotational VOR, have as their major role the stabilization of the visual axes in space in response to unexpected perturbations. The otoliths are excited by linear acceleration (Fernández and Goldberg, 1976), with the saccule mainly excited by vertical acceleration and the utricle by acceleration in the horizontal plane, corresponding to their orientations in the skull. In the case of the utricle, excitation can occur either by linear acceleration to one side or, through the action of gravity, tilt to the other. The appropriate response to these two types of disturbance may be quite different and how this ambiguity is resolved has not been fully understood. VEMPs evoked by impulsive stimuli, such as a tendon hammer tap or an impulse from a minishaker, represent phasic accelerations similar to those that occur physiologically during normal movements of walking and running (Pozzo et al., 1991).
Otolith-ocular reflexes in response to linear accelerations in the horizontal plane, reflecting utricular sensitivity, may induce either tilt reflexes or a translational linear VOR (LVOR). The former is the appropriate response to a tilt, the latter to a linear translation. The translational LVOR is a relatively recent discovery (Angelaki, 2004), and the two reflexes may even originate from different parts of the utricle (Leigh and Zee, 2006). Whole-body linear acceleration, a situation that should favor the translational LVOR, evokes little torsion (Aw et al., 2003), but does evoke a horizontal ocular movement beginning at just over 30 ms. Given the structure of the head and neck – crudely, a weight on a support – one might expect that linear accelerations of the head itself would most often represent tilts and that pure linear translations would be rarer. The tonic otolith-ocular tilt reflex is thought to have a low gain, and a low-pass frequency response, but this may apply only to the tonic reflex. Colebatch et al. (2014) concluded that oVEMPs evoked by impulsive lateral head translation were likely to represent tilt VOR responses, based in part on the patterns of torsion obtained. Given that the trunk was fixed in these experiments, such a physiologic response would be appropriate. On the other hand, Todd et al. (2012), who studied oVEMPs evoked by fore–aft linear accelerations of the whole body, concluded that these were likely to be manifestations of the translational LVOR.

Vestibulocollic reflexes are best characterized for rotations, while linear acceleration effects are less well characterized (Goldberg and Cullen, 2011). Utriculocollic reflexes have been reported to facilitate ipsilateral neck flexors and extensors, consistent with a role in the LVOR (Ikegami et al., 1994), although the opposite connectivity has also been reported (Wilson et al., 1977). Impulsive lateral head accelerations evokeocular responses more consistent with the tilt reflex than the LVOR (Colebatch et al., 2014). AC stimuli predominantly excite saccular afferents and evoke an inhibitory response in the SCM (Colebatch and Rothwell, 2004). Both whole saccular nerve (Goto et al., 2004) and AC stimuli evoke an upwards eye movement, although this is not invariable (Todd et al., 2007; Welgampola et al., 2009). These findings are consistent with a saccular reflex to compensate for sudden head drops. Saccular reflexes also appear to be related to changes in gait speed with age (Layman et al., 2015).

**METHODODOLOGY FOR RECORDING CVEMPS AND OVEMPS**

**Stimuli and safety**

The recording equipment for VEMPs is similar to other devices used for clinical neurophysiologic studies. AC sound is the typical cVEMP stimulus and is particularly suited to diagnosing superior canal dehiscence (SCD). AC stimuli must be generated using calibrated equipment because the intensities used are high and could be potentially harmful to hearing if not controlled. Peak intensity values are preferable to root mean square levels as safe limits are specified in these units. Ideally sound intensity should be measured using specific equipment, but for the TDH49 headphones a “nominal” calibration of 140 dB SPL for 5 V input can be assumed to be correct within 1–2 dB (manufacturer’s specifications). The most widely used AC stimuli are 500 Hz tone bursts or 0.1 ms clicks. Using brief stimuli, not exceeding 140 dB SPL peak intensity for AC stimulation and minimizing stimulus repetitions should ensure that there are no adverse effects on hearing (Colebatch and Rosengren, 2014). Calibration in SPL is also preferable to HL as this measure, as well as the safe limits of exposure, is better defined using SPL intensities. Tone bursts between about 400 and 1000 Hz produce larger reflexes than clicks delivered with the same sound energy due to tuning effects. However, care is required when setting the intensity and duration of the stimulus, as the total energy content of the waveform needs to be considered (Rosengren et al., 2009).

BC stimulation was initially achieved using bone oscillators like the B71, but currently a minishaker such as the Bruel and Kjaer model 4810 is preferred for its greater output and frequency range. However, for both, a suitable amplifier is needed. Stimulus intensity, frequency, and duration should be specified. Calibrating the 4810 or other minishaker in force level requires an artificial mastoid. The phase of movement must be determined (i.e., whether a positive voltage moves the shaft toward or away from the motor), as this is not uniform. The most widely used BC stimuli are 500-Hz tone bursts delivered to the midline at AFz, Fz, or to the mastoids (Sharbrough et al., 1991). The mastoid is very suitable for reflexes evoked by tendon hammer taps or impulsive lateral stimulation. For 500 Hz BC stimulation there is little benefit to be gained in terms of amplitude by using more than one cycle (Lim et al., 2013). Brief stimuli with short rise times are also preferable as they minimize electromechanical stimulus artefact and produce responses with short, tightly grouped latencies. Due to the sensitivity of VEMPs to the direction of head acceleration, BC stimuli should be delivered with fixed polarity, while for AC stimulation the polarity can be alternated to reduce stimulus artefacts. For BC stimulation, a positive polarity, i.e., one which accelerates the minishaker rod toward the skull (similar to a tendon hammer), typically produces shorter latencies.

From the earliest observations it has been clear that stimulus intensity is a critical factor in evoking a cVEMP. Dennis et al. (2014) showed that the p13 and n23 responses were not well fit using linear regression of reflex amplitude against stimulus intensity (in dB) but
rather, an acceptable linear response was obtained when the log of the reflex amplitude was used, implying a power law relationship (Todd et al., 2008a). For the oVEMP, the amplitude in normal subjects also follows a power law, although this only applies to the n10-p15 response once a threshold has been exceeded (Dennis et al., 2014).

cVEMP methodology

Recently there has been an attempt to develop standardization of cVEMP methodology (Papathanasiou et al., 2014). Surface electrodes should be applied using an active-reference montage, with the active electrode ideally positioned over the motor point of the muscle or nearby (Colebatch, 2012) and the reference over the medial or lateral clavicle. Asking subjects to rotate their heads makes the muscle easy to visualize. EMG amplification by around 2000× (66 dB) and filtering between 10 Hz and 2 kHz are typical. Usually 100–200 stimulus presentations are averaged. Peri-trigger recording (i.e., recording some EMG prior to the stimulus) is desirable to assess the level of background “noise” as well as to estimate the level of tonic muscle activation, free of any evoked response. The most critical elements in recording cEMPs are the stimulus type and intensity (discussed above) and the degree of activation of the SCM and its measurement. Although there are semiquantitative approaches to controlling the level of muscle contraction (e.g., pressing on a blood pressure cuff), that should improve the symmetry of activation on the two sides (Vanspauwen et al., 2006), quantitative methods are to be preferred, as they provide a direct measurement of muscle activity. They also produce values that can be compared between laboratories. A relatively simple method of correcting for differences in muscle activity is to divide the p13-n23 peak-to-peak amplitude by the level of full-wave rectified and averaged EMG derived from the same recording electrodes (Fig. 10.5). This method ignores any offset to the relationship between amplitude and activation and a certain level of activation is required to ensure reliable measurements (Rosengren, 2015). An elementary error is to calculate the full-wave rectified value after averaging – this leads to an underestimation of the true level of full-wave rectified activity and produces values that depend upon the number of trials averaged.

Fig. 10.5. Unrectified average (upper half) and full-wave rectified average (lower half) from sternocleidomastoid. The stimulus was given at time 0, 20 ms after the onset of the average. The prestimulus period serves two functions. In the upper, unrectified average, a flat baseline with little electromyogram (EMG) “noise” enables clear identification of the p13 and n23 peaks. In the lower, rectified average, the prestimulus period is used to determine the average level of activation (mean rectified EMG), unaffected by any evoked response. A simple method to correct for differing levels of activation is to express the p13-n23 amplitude as a ratio of the mean rectified activity, here giving 2.34 (225/96). Note the level of rectified activity is sufficient to give reliable corrected values (Rosengren, 2015). (Modified from Rosengren et al., 2010.)
oVEMP methodology

The oVEMP has broadly similar stimulation and recording requirements to the cVEMP (Fig. 10.3), though some stimuli are less suitable for oVEMPs. In particular, while BC stimulation produces robust cVEMPs in most normal volunteers, oVEMPs evoked by AC stimulation are small, have a higher threshold, and are often absent, especially in older patients. The high rate of absent responses for AC oVEMPs is a significant problem for its clinical application. While oVEMPs evoked by BC stimulation are typically larger and more robust, this depends on stimulus properties.

oVEMPs are usually recorded from a pair of electrodes placed beneath the eye in a vertical line. This bipolar arrangement reduces the potential impact of distant sources and provides a more selective recording of IO muscle activity than a referential montage (Todd et al., 2007). Alternative montages have recently been investigated, e.g., with the active electrode placed more laterally, and have found larger, though more variable, amplitudes (Sandhu et al., 2013). The advantage of the standard montage is that it appears to provide a relatively pure recording of the IO muscle, which receives a crossed projection from the otoliths.

OEMPs can be recorded with the patient seated upright or reclined. The more critical factor is the level of gaze elevation, which is best kept above approximately 20°. Gaze can be standardized at a fixed angle by providing visual targets, or maximized by asking subjects to look upwards as far as possible. In clinical contexts, the test should be repeated using maximal gaze if the oVEMP is absent when first tested at a lower gaze angle. While factors such as fatigue, nystagmus, head tilt, and alcohol intoxication can have attenuating effects on oVEMP amplitude, the reflex is not abolished by these conditions as long as a sufficient degree of up-gaze is maintained during the test (Lin and Young, 2014; Rosengren et al., 2014). Although the oVEMP is not a blink reflex, patients often blink during the first couple of stimuli. However, these responses habituate very quickly under typical recording conditions and only very rarely contaminate the average. The initial trials can be deleted to avoid this.

As the oVEMP is approximately an order of magnitude smaller than the cVEMP, a higher gain is required. The frequency content of the oVEMP is higher than the cVEMP, as the reflex tends to oscillate at about 100 Hz, and thus low-pass filter settings should be the same as or higher than for the cVEMP. The recording window can be the same or shorter than for the cVEMP, and it is useful to include a pre-stimulus recording to help confirm that the baseline is sufficiently flat to ensure the recorded peaks are reliable.

VEMP measurement

For the cVEMP, the p13 and n23 components of the cVEMP are measured at the response peaks. Peak-to-peak amplitude is calculated, and is corrected for the level of tonic activation when possible, giving a dimensionless ratio (or corrected amplitude). For the oVEMP, the first biphasic components are usually measured: either the n10 or the n10-p15 peak-to-peak amplitude. For both reflexes, amplitude and symmetry are usually the main measurements of interest, but note should also be made of the latency of the peaks and their threshold (if SCD is suspected). Symmetry is typically calculated by the Jongkees formula: (larger – smaller)/(larger+smaller). The smaller amplitude is usually the abnormal one, but not invariably (e.g., SCD causes enlarged responses). Latency is most relevant to central abnormalities.

As stimulus properties such as intensity, frequency, shape, duration, and rise time have significant effects on the normal ranges of amplitude and latency for both cVEMPs and oVEMPs, it is recommended that clinics establish their own normative data sets.

ROLE IN DIAGNOSIS

An abnormality affecting the cVEMP or oVEMP indicates a lesion along the vestibulocollic (cVEMP) or vestibulo-ocular (oVEMP) reflex pathways. Unilateral absence of both responses localizes the lesion to the end organ, primary afferents, or nerve root entry zone (assuming there is no conductive hearing loss if an AC stimulus is used). Delayed latencies for both reflexes can be encountered in demyelinating neuropathies affecting the vestibular nerves or in central disorders. Using three-dimensional video head impulse test (vHIT), oVEMPs, and cVEMPs, it is now possible to test all five vestibular end organs noninvasively. VEMPs, particularly when combined with vHIT, calorics, and audiometry, will often produce a characteristic disease profile that enables diagnosis of the underlying vestibular disorder.

Superior canal dehiscence and third-window syndromes

Very soon after the initial report of the cVEMP, it became clear that subjects with what was then called Tullio syndrome – sound-induced vertigo and nystagmus – showed specific changes on VEMP testing, namely, reduced thresholds. Colebatch et al. (1998) reported that 7 patients with symptoms and signs of Tullio phenomena all showed lower thresholds for their cVEMPs than for their asymptomatic ears or for 25 controls. Galvanic-induced sway responses were essentially normal, localizing the abnormality to the periphery. This syndrome is now recognized to be nearly always due to a defect in
the bone overlying the superior semicircular canal (Minor et al., 1998) and, while this may be recognized radiologically, it is not always clear whether the radiologic changes are of functional significance (e.g., Watson et al., 2000). A typical abnormality on VEMP testing confirms that the radiologic finding is likely to be functionally significant (Fig. 10.6).

Amplitudes of cVEMPs are increased but overlap with normal values (Brantberg et al., 1999; Rosengren et al., 2008; Welgampola et al., 2008), probably as a consequence of it being an inhibitory reflex. Responses at abnormally low thresholds have however been repeatedly confirmed for SCD using AC stimuli (Fig. 10.6). Zhou et al. (2007) evaluated 65 patients for possible SCD and found that abnormal AC cVEMPs showed over 90% sensitivity and specificity. One patient with low thresholds had posterior canal dehiscence, indicating that the VEMP changes are indicative of an abnormal “third window” and not, strictly, its location. Welgampola et al. (2008) showed significantly reduced thresholds for cVEMPs (similar to those for oVEMPs) in patients with SCD and, importantly, reported that the thresholds returned to normal with successful treatment (see also Niesten et al., 2013). Roditi et al. (2009) agreed that abnormal cVEMPs were a better indicator of disturbed physiology than radiologic findings alone and pointed out the value of the cVEMP in bilateral cases. Brantberg and Verrecchia (2009) reported that showing a large-amplitude response to a weak AC stimulus, below the level of saturation, can be as effective as measuring the actual thresholds.

With the development of the oVEMP, an excitatory reflex, it became clear that amplitude differences shown with oVEMPs were a more reliable guide to SCD than for the cVEMP. Rosengren et al. (2008) and Welgampola et al. (2008) both showed that the amplitudes of AC- and BC-evoked oVEMPs at standard stimulus intensities were much higher when compared to controls than were cVEMP amplitudes, but had similar thresholds. The high oVEMP amplitudes in SCD are likely to be due in part to an effect of superior canal afferents themselves, whose thresholds to sound stimulation drop dramatically with experimental dehiscence (Carey et al., 2004). BC stimuli also show abnormalities in SCD, although the threshold reductions appear to be less marked than for AC stimuli (Welgampola et al., 2008). The optimum stimulus has not been extensively investigated and higher frequencies than those normally used may be even more specific (Zhang et al., 2011b, 2012b; Manzari et al., 2013).

VEMPs appear to have an established role in the management of patients with SCD. The demonstration of pathologic sound sensitivity confirms the significance of radiologic findings and can be a guide to the symptomatic side in bilateral cases. Pre- and postoperative observations can confirm the effectiveness of surgery. VEMP testing, and thereby consideration of SCD as an alternative diagnosis, should be considered in cases of suspected otosclerosis and perilymph fistula where operative treatment is considered necessary, as SCD may mimic features of these conditions.

Reduced thresholds are not unique to SCD. Large vestibular aqueducts are associated with mildly reduced VEMP thresholds to AC stimuli (Sheykholeslami et al., 2004; Merchant et al., 2007; Taylor et al., 2012b). A minority of patients with perilymph fistulas have the Tullio phenomenon, loosely defined (Fox et al., 1988), and a case of perilymph fistula with a low-threshold VEMP has been reported (Hermann and Coelho, 2014), although it is not clear if this is typical. Both these conditions need to be considered in the differential diagnosis of low AC thresholds. Conversely, the presence of SCD or the rarer posterior canal dehiscence (Aw et al., 2010) needs to be considered in all cases with unequivocably abnormally low thresholds.

**Acute vestibular syndromes**

**Vestibular neuritis**

Presenting with sudden severe and prolonged vertigo without hearing loss, unidirectional spontaneous
nystagmus, and a positive HIT, vestibular neuritis is an acute, self-limiting vestibulopathy. The dysfunction is selective and usually affects the afferents traveling in the superior division of the vestibular nerve more severely than those in the inferior division (Fetter and Dichgans, 1996; Fig. 10.7). As a consequence, the cVEMP is usually relatively spared (Murofushi et al., 1996), while the oVEMP is attenuated or abolished, whether evoked by 500 Hz stimuli via AC or BC origin (Govender et al., 2011, 2015). If the whole nerve is affected or in the much rarer inferior form of vestibular neuritis, the cVEMP is attenuated (Halmagyi et al., 2002; Kim and Kim, 2012). The pattern of involvement of the oVEMP, the cVEMP, or both can indicate superior, inferior, or pan vestibular neuritis (Govender and Colebatch, 2011).

Fig. 10.7. Typical findings for vestibular neuritis affecting the superior division of the left vestibular nerve. Stimulation of the left ear evokes a normal cervical vestibular-evoked myogenic potential (cVEMP; asymmetry ratios given in parentheses; CA, corrected activity) but no ocular VEMP (oVEMP). Right-sided stimulation is normal. Below are shown the typical findings for the visual head impulse test (reduced gain of the left horizontal and anterior canals), the ipsiversive deviation of the subjective visual horizontal (SVH) on repeated measurements and the (normal) audiogram. BC, bone-conducted; AC, air-conducted; RH, LH, right and left horizontal canal; RA, LA, right and left anterior canal; RP, LP, right and left posterior canal; HL, hearing loss.
Magliulo et al. (2014) studied 40 subjects with vestibular neuritis within 10 days of symptom onset, using vHIT, cVEMPs to AC 500 Hz tones and oVEMPs to BC stimuli, and reported that 55%, 40%, and 5% of subjects had complete, superior, and inferior vestibular neuritis. These authors used raw cVEMP amplitudes and an amplitude criterion (rather than an asymmetry ratio) for determining the normality of VEMPs. While 80% of subjects had absent or reduced oVEMPs on the affected side, only 47.5% had absent or reduced cVEMPs. A study of acute vestibular neuritis (within 2–5 days of onset) by Walther and Blödow (2013), which also used raw cVEMP amplitudes, showed absent or asymmetric AC oVEMPs and AC cVEMPs in 65% and 40% of subjects. In a retrospective review of 703 patients with acute vestibular neuritis, Kim and Kim (2012) reported 9 subjects with inferior vestibular neuritis, most of whom had spontaneous torsional downbeating nystagmus, impaired posterior vHIT (n = 7) and absent or asymmetric AC cVEMPs (6 of 8) but preserved oVEMPs (4 of 4).

Govender et al. (2015), in a predominantly prospective study, showed that both AC and BC 500 Hz stimulus-evoked oVEMPs showed similar sensitivities for the detection of vestibular neuritis – with over 80% abnormalities for AC-evoked oVEMPs, the majority of whom had cVEMPs amplitude ratios within the normal range. The use of both modalities of stimulation improved sensitivity. Impulsive stimuli, such as head taps, show more abnormalities of the cVEMP in vestibular neuritis (Brantberg et al., 2003; Govender et al., 2011, 2015), presumably due to strong activation of utricular afferents projecting to the SCM. The cVEMP also appears to be more often abnormal with herpes zoster oticus, particularly if patients have vestibular symptoms (Lu and Young, 2003).

**Brainstem and cerebellar stroke.**

Strokes could potentially affect VEMP pathways by infarction of the labyrinth, vestibular nuclei, or vestibulospinal tracts. An early study that compared cVEMPs in controls, isolated cerebellar strokes (n = 19), and brainstem strokes (n = 15) reported no abnormalities in cerebellar strokes and a low prevalence of delayed peak latencies (n = 2) in brainstem stroke (Pollack et al., 2006). Later, Choi et al. (2014) found a 41% and 33% prevalence in cVEMP and oVEMP abnormalities in isolated cerebellar infarcts, with a nearly threefold increase in the prevalence of abnormalities in those patients who also had an ocular tilt reaction signifying involvement of the graviceptive pathways.

Both posterior inferior cerebellar artery (PICA) and anterior inferior cerebellar artery (AICA) strokes can present as acute vestibular syndromes, usually accompanied by additional physical signs that enable their recognition. Weng and Young (2014) found abnormal cVEMPs in 36% and 75% of tested ears in PICA and AICA strokes; oVEMPs were abnormal in 57% of PICA and 50% of AICA ears tested. Hearing loss (commonly observed in AICA stroke) was a better separator of these two syndromes than the pattern of VEMP abnormalities. Ahn et al. (2011) also found a 50% prevalence of absent or asymmetric AC cVEMPs in AICA strokes, in addition to hearing loss and canal paresis on caloric testing. Isolated vestibular nucleus infarction can occur with either PICA or AICA stroke and may present with isolated spontaneous vertigo and horizontal-torsional spontaneous nystagmus and, sometimes, bidirectional gaze-evoked nystagmus. Kim et al. (2014) reported 2 such patients, both of whom had significant ipsilesional AC cVEMP and oVEMP asymmetry and bilateral (ipsilesional > contralesional) head impulse deficits in horizontal and posterior canal planes.

Recently Oh et al. (2013) undertook a large study (n = 52) of AC oVEMPs in brainstem lesions inclusive of strokes, in which they found a 54% prevalence of abnormalities, mostly when the lesions occupied the dorsomedial brainstem. They hypothesized that involvement of the medial longitudinal fasciculus, crossed ventral tegmental tract, and oculomotor nuclei were responsible for these abnormalities. Heide et al. (2010) examined AC cVEMPs in 29 subjects with brainstem stroke and reported 41% abnormalities mostly localized to the dorsolateral medulla or lateral part of the lower pons. They attributed these findings to lesions affecting the spinal accessory nucleus and vestibular nucleus.

**Episodic and recurrent vertigo.**

Menière’s disease (MD) is characterized by attacks of vertigo lasting from minutes to hours, with fluctuating low-frequency cochlear hearing loss, tinnitus, and aural pressure. Early MD before the onset of aural symptoms (“vestibular MD”) is difficult to separate from vestibular migraine (VM). Ipsilesional reduction in AC cVEMP reflex amplitude has been widely reported in MD, with a prevalence of 35–55% (de Waele et al., 1999; Huang et al., 2011; Taylor et al., 2011). When AC cVEMPs are bilaterally present in MD, the ear with the smaller cVEMP is not necessarily the affected one: the AC cVEMP can be augmented in early MD (Young et al., 2002), perhaps because the hydropic sacculus presses against the stapes footplate, enhancing saccular sensitivity to AC sound. An enhanced cVEMP with an ipsilateral canal paresis may suggest early MD (unpublished observations). As the disease advances, cVEMPs tend to disappear (Young et al., 2003), but can reappear or become
enlarged with glycerol or furosemide, which are drugs that would be expected to reduce endolymphatic hydrops (Murofushi et al., 2001; Seo et al., 2003; Ban et al., 2007). Fluctuation of the cVEMP during an acute attack, i.e., disappearance or attenuation of cVEMPs during the first 24 hours after symptom onset and reappearance of responses after 48 hours, has also been documented (Kuo et al., 2005). Rauch et al. (2004), using tone bursts with a two-cycle rise and fall delivered at 13 Hz, recorded the lowest average cVEMP thresholds at 500 Hz in controls. Compared with controls, affected MD ears had significantly increased cVEMP thresholds and less tuning at 500 Hz. Even unaffected ears of MD subjects showed elevated thresholds compared with normal subjects. Kim-Lee et al. (2009) observed that the frequency peak amplitude ratio, i.e., the ratio between raw peak-to-peak cVEMP amplitudes at 1000 Hz and 500 Hz, lies above 0.7 in 93.5% of MD ears and falls below 0.7 in 95% of controls. Winters et al. (2011) examined AC oVEMP tuning characteristics in controls and MD and recorded the highest amplitudes and lowest thresholds at 500 Hz followed by 1000 Hz. In affected ears of MD patients, the optimal frequency had shifted to 1000 Hz. Tuning alterations may prove a diagnostically useful reflex measure in MD. AC oVEMPs, AC cVEMPs, BC cVEMPs, and BC oVEMPs are abnormal in MD in a descending order of prevalence (Huang et al., 2011; Taylor et al., 2011).

**VESTIBULAR MIGRAINE**

VM can present with episodic spontaneous or positional vertigo lasting seconds to days. Studies that examine VEMP attributes in VM are few and are mostly based upon data collected prior to the publication of the Bárány Society’s diagnostic criteria (Lempert et al., 2012). Baier et al. (2009) recorded cVEMPs to 400 Hz / 100 dB normal HL tone bursts and found bilateral reduction in VEMP amplitudes when compared with age- and gender-matched controls, but did not statistically compare VEMP asymmetry ratios. Zaleski et al. (2015) compared AC cVEMPs and oVEMPs in VM patients and controls. Subjects with VM had no significant differences in raw cVEMP amplitudes, amplitude asymmetry, or latencies. In contrast, oVEMP prevalence was lower in VM compared with controls (72% vs. 100%) and amplitude asymmetry was significantly higher. Taylor et al. (2012c), in contrast, found no significant differences in AC click- and BC tap-evoked cervical and ocular VEMPs between VM and controls. Using tone bursts at octave frequencies between 250 and 2000 Hz, cVEMP and oVEMP were compared in controls, VM, and MD. For both the oVEMP and cVEMP, frequency tuning characteristics of VM did not differ significantly from age-matched controls. The optimal frequencies for VM, unaffected MD ears, and controls were 500 Hz and 1 kHz, but affected MD ears tuned to 1 kHz. The ratio of cVEMP amplitudes at 0.5 and 1 kHz, VEMP asymmetry ratio using 0.5 kHz stimuli, and caloric tests combined separated VM from MD with a sensitivity of 90.0% and specificity of 70.0%.

**Benign paroxysmal positional vertigo**

Benign paroxysmal positional vertigo (BPPV) is characterized by a unique positional nystagmus profile that enables bedside diagnosis. An early study by Murofushi et al. (1996) reported that in BPPV secondary to (superior) vestibular neuritis, AC cVEMPs were usually preserved, as the inferior vestibular nerve, which innervates both the saccule and the posterior canal, has to be intact in order to generate vertigo by activation of posterior-canal afferents.

AC cVEMPs with ipsilaterally absent, attenuated, or delayed responses have since been identified in up to 52% of posterior-canal BPPV patients (Akkuzu et al., 2006; Hong et al., 2008; Korres et al., 2011; Eryaman et al., 2012), but methodologic issues, including variability in control of SCM activation, small sample sizes, and patient selection criteria, limit the interpretation of these findings. A study by Lee et al. (2013) that did not specifically separate idiopathic from secondary causes of BPPV reported a 10% prevalence of abnormal oVEMPs or cVEMPs in nonrecurrent BPPV but 25% and 30% prevalence in recurrent BPPV. Yang et al. (2008) found absent AC cVEMP responses as well as delayed p13n23 latencies when compared with controls. Although the number of maneuvers required to treat did not correlate with the degree of latency prolongation, absent VEMPs did correlate with a greater number of treatments. There is a report that otolith function may improve following particle repositioning (Seo et al., 2013).

**Other peripheral and central vestibular abnormalities**

**Gentamicin treatment**

Intratympanic gentamicin injections are used to treat intractable vertigo in MD. In most patients, AC cVEMPs are reported to be within the normal range before treatment and are very often abolished following treatment, frequently after only a single dose (de Waele et al., 2002; Picciotti et al., 2005; Helling et al., 2007; Ozluoglu et al., 2008). The posttreatment AC cVEMP was more often abolished than the caloric response or shift in subjective visual vertical, suggesting that the saccule may be more sensitive to gentamicin than other parts of the vestibule (Picciotti et al., 2005; Helling et al.,
However, the AC cVEMP was not correlated with residual vertigo attacks, indicating that it is not a reliable indicator of treatment success. In a study comparing AC with GVS stimulation, after a single injection 92% of ears lost cVEMPs to AC sound, while 32% and 46% lost cVEMPs to low-intensity GVS at 1 month and 2 years (de Waele et al., 2002). Although the caloric responses and vertigo attacks returned over time in some patients, this did not occur in patients with abolished GVS cVEMPs, suggesting that the GVS cVEMP may be a useful indicator of adequacy of gentamicin ablation. The AC cVEMP is also likely to be abolished in systemic aminoglycoside toxicity and could potentially be used to non-invasively monitor patients receiving aminoglycoside therapy.

**Bilateral Vestibulopathy**

Bilateral vestibulopathy may be the consequence of ototoxic aminoglycosides, bilateral MD, meningitic processes, autoimmune or idiopathic disorders. VEMPs may constitute a useful component of vestibular assessment in these patients, but their preservation does not prevent vertical oscillopsia (Brantberg and Löfqvist, 2007).

**Multiple sclerosis**

cVEMP abnormalities are present in 31–70% of patients with multiple sclerosis, often consisting of delays (Shimizu et al., 2000; Versino et al., 2002; Alpini et al., 2004; Bandini et al., 2004; Patkó et al., 2007), and in most studies there is little correlation with radiologic findings. oVEMPs ascend to the midbrain and are frequently abnormal in the presence of internuclear ophthalmoplegia (Rosengren and Colebatch, 2011). Gazioglu and Boz (2012) found a 45% abnormality rate for oVEMPs and only 18% for cVEMPs in a group of 62 patients with definite multiple sclerosis. Rates of abnormality were higher with signs or a history of brainstem involvement and with higher disability.

**Hearing loss with imbalance/vertigo**

**Vestibular schwannomas and cerebellopontine angle meningiomas**

Studies that combine cVEMPs and oVEMPs indicate that both responses can be abolished or attenuated in subjects with schwannoma, with similar prevalences of ~50–70% for AC cVEMP and BC oVEMP (Kinoshita et al., 2013; Chiarovano et al., 2014; Taylor et al., 2015). The prevalence of both VEMP modalities is significantly correlated with maximal tumor diameter. Neither test correlates with the nerve of origin of the vestibular schwannoma at surgery (Suzuki et al., 2008). Large and medium-sized tumors (>14 mm in diameter) most commonly demonstrate vestibular test abnormalities referable to both divisions of the vestibular nerve (92%) and only rarely point to involvement of a single division (Taylor et al., 2015). AC cVEMPs may also be abolished or attenuated in schwannoma patients with normal brainstem-evoked potentials (Matsuzaki et al., 1999) and even in patients with normal audiometry (Taylor et al., 2015). Thus, VEMPs constitute a valuable addition to the noninvasive test battery that should be offered to patients presenting with symptoms such as monaural tinnitus, muffled hearing loss, and unexplained imbalance suspicious for a schwannoma. A single small study that compared cerebellopontine angle meningiomas and schwannomas found a similar prevalence of VEMP abnormalities in these two tumors (Su et al., 2013).

CVEMPs and oVEMPs in conjunction with threedimensional vHIT could prove valuable when evaluating residual vestibular function before schwannoma surgery. Since those with near-normal preoperative function could be at risk of developing an acute and perhaps a chronic unilateral vestibular deafferentation syndrome, having these test profiles could help surgeons plan pre- and postoperative management. Controlled vestibular deafferentation with intratympanic gentamicin before surgery, followed by vestibular pre-habilitation, has been validated as a method of minimizing postsurgical vestibular symptoms (Magnusson et al., 2007).

**Otosclerosis and middle-ear disease**

Disease of the middle ear and its contents usually leads to conductive hearing loss and an air–bone gap of 15 dB or more leads to attenuation of AC VEMPs (Halmagyi et al., 1994). Otosclerosis is characterized by conductive hearing loss, absent acoustic reflexes, and, less commonly, vertigo. AC cVEMPs are frequently absent but may be recordable in 21–29% of ears. The likelihood of AC VEMP attenuation is proportional to the degree of conductive hearing loss (Tramontani et al., 2014). Subjects with otosclerosis who develop vertigo and imbalance have a significantly higher prevalence of BC cVEMP abnormalities (absent responses: 90%) than those who are symptom-free (6.6%), indicating that otosclerosis could affect otolith function, thereby attenuating the VEMP (Saka et al., 2012).

The use of VEMPs allows the recognition of inner-ear causes of apparent conductive hearing loss (e.g., Picavet et al., 2009). Zhou et al. (2012) found that VEMP thresholds correctly classified all but 3 of 120 patients with air–bone gaps into either middle-ear pathology or inner-ear and other pathology, the latter including SCD and enlarged vestibular aqueducts.
SUDDEN HEARING LOSS AND VERTIGO

Sudden sensorineural hearing loss refers to a 30 dB or greater increase in hearing threshold across three or more adjacent frequencies within a period of 24–72 hours and could be caused by disorders affecting the entire labyrinth (labyrinthitis), ischemia affecting the labyrinthine artery, or immune-mediated inner-ear disorders. Iwasaki et al. (2005) reported a high prevalence of AC cVEMP abnormalities (77%) in sudden sensorineural hearing loss when compared with caloric asymmetry (45%). Based upon the preservation of galvanic cVEMPs in all tested patients, they hypothesized the labyrinth to be the site of the lesion. Nagai et al. (2014) found a higher prevalence of asymmetric AC cVEMP (41.5%) compared with BC oVEMPs (9.3%), while Fujimoto et al. (2015) found cVEMPs, oVEMPs, and calorics to be abnormal in 64%, 43%, and 52% of subjects respectively. Absence of oVEMPs was associated with a poorer prognosis in the study of Nagai et al. (2014).

CONCLUSION

In the 20 or so years since its initial description, the VEMP – to date, principally the AC cVEMP – has established an important role in the diagnosis and assessment of vestibular disorders. One clear contribution is in the recognition, assessment, and differential diagnosis of “third-window” abnormalities. However, its contribution is such that VEMP testing has a role as an additional imaging correlate. Mult Scler 10: 316–321.


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